



Practitioner's Docket No. U 014868-8

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: OM DUTT TYAGI, et al

Application No.: 10/694,619

Group No.: 1614

Filed: OCTOBER 27, 2001

Examiner:

For: METHOD FOR PREPARATION OF CEFTIOFUR AND SALTS THEREOF

Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: INDIA

Application
Number: 938/MUM/2002

Filing Date: OCTOBER 29, 2002

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)

I hereby certify that this correspondence is, on the date shown below, being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Date: February 23, 2004

Signature

JANET I. CORD

(type or print name of person certifying)


SIGNATURE OF PRACTITIONER

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NOTE: *"The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).*

ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)



(1) We, LUPIN LIMITED, a Company incorporated under the Companies Act, 1956, of 159 CST Road, Kalina, Santacruz (East), Mumbai - 400 098, Maharashtra, India

(2) hereby declare -

(a) That we are in possession of an invention titled

"AN IMPROVED METHOD FOR PREPARATION OF CEFTIOFUR AND SALTS THEREOF"

(a) that the Complete/Provisional Specification relating to this invention is filed with this application;

(b) that there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that the inventors for the said invention are:

(1) TYAGI, Om dutt; (2) RICHHARIYA, Santosh Kumar; and (3) PAWAR, Rajesh Kumar Ramchandra; all Indian citizens of Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune-411 042, Maharashtra, India

(4) We claim priority from the application filed in the following convention country, particulars of which are as follows:

NIL

(5) That we are the assignees of the true and first inventors.

(6) That our address for service in India is as follows:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
E 556, Greater Kailash II,
New Delhi - 110 048, India.
Phone: 91 11 628 5603/6012/6025
Facsimile: 91 11 6286005
Email: sna@vsnl.com

(7) Following declaration was given by the inventors:

We, (1) TYAGI, Om Dutt; (2) RICHHARIYA, Santosh Kumar; and (3) PAWAR, Rajesh Kumar Ramchandra; all Indian citizens of Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune-411 042, Maharashtra, India, the

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MUM

DUPLICATE

true and first inventor for this application declare that the applicants herein are our assignees.

TYAGI, Om Dutt

RICHHARIYA, Santosh Kumar

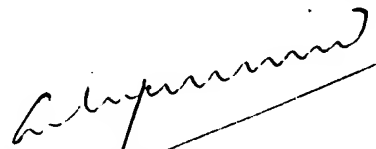
PAWAR, Rajesh Kumar Ramchandra

- (8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to me/us on this application.
- (9) Following are the attachments with this application:
- (a) Provisional specification in triplicate
 - (b) Application forms 1 in triplicate
 - (c) Statement and Undertaking on FORM 3 in duplicate
 - (d) Drawings in triplicate
 - (e) Abstract

Fee Rs. in Cash/Cheque/Bank Draft Bearing No.....
dated.....onBank.

We request that a patent be granted to us for the said invention.

Dated this 26th day of October 2002



LUPIN LIMITED

The Controller of Patents
The Patent Office,
At Mumbai



Form 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION (Section 10)

**"AN IMPROVED METHOD FOR THE PREPARATION OF CEFTIOFUR AND SALTS
THEREOF"**

LUPIN LIMITED, a company organised and existing under the Companies Act, 1956, of 159,
CST Road, Kalina, Santacruz (East), Mumbai-400 098, Maharashtra

The following specification describes the nature of the invention:

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FIELD OF THE INVENTION

COC(=O)N=C(c1nc(N)s1)C(=O)Nc2c(=O)[nH]c3c2sc(CSc4cc5ccccc5o4)c3C(=O)OC

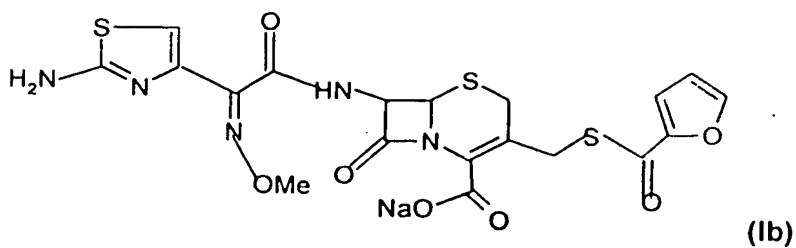
(1)

BACKGROUND OF THE INVENTION

COC(=O)N=C(c1nc(N)s1)C(=O)Nc2c(s3c(=O)[nH]c23)C(=O)c4cc(=O)[nH]4CCSC(=O)c5ccoc5

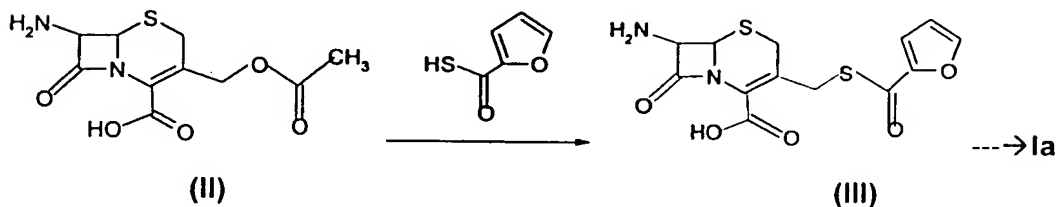
(1a)

and its sodium salt of formula (Ib)

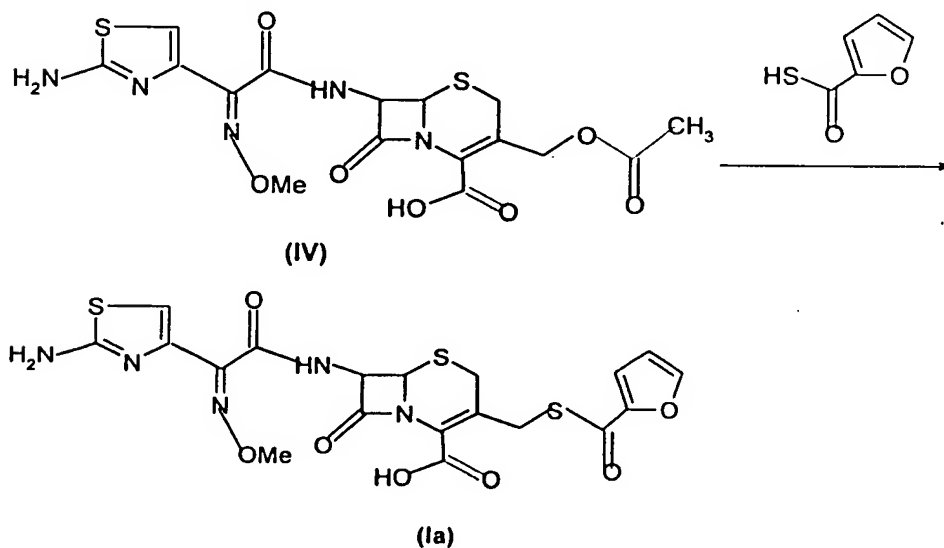


1. US Patent No. **US 4464367**, which covers ceftiofur sodium, discloses two methods for preparation of the same, viz.

i) reaction of 7-amino-cephalosporanic acid (7-ACA) of formula (II) with thiofuroic acid to give the 3-thio-methyl substituted derivative (III), which is further elaborated to give ceftiofur (Ia) as shown below



ii) reacting 7-[2-(2-amino-4-thiazolyl)-2-methoxyimino acetamido] cephalosporanic acid, generically known as cefotaxime of formula (IV) with thiofuroic acid to give ceftiofur (Ia) as shown below:



The mineral salts of the corresponding acids are obtained by action on the free acid of a mineral base such as NaOH or KOH or NaHCO₃ in equimolar quantity; the salification reaction is effected in a solvent such as water or ethanol and the salt obtained is isolated by evaporation of the solution.

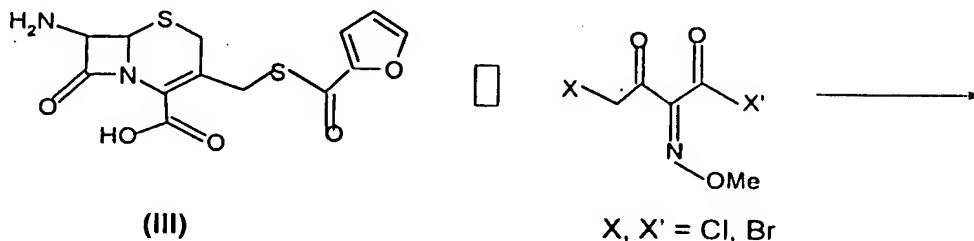
However, US 4464367 does not provide any sufficient details or enabling conditions for preparation of ceftiofur from cefotaxime.

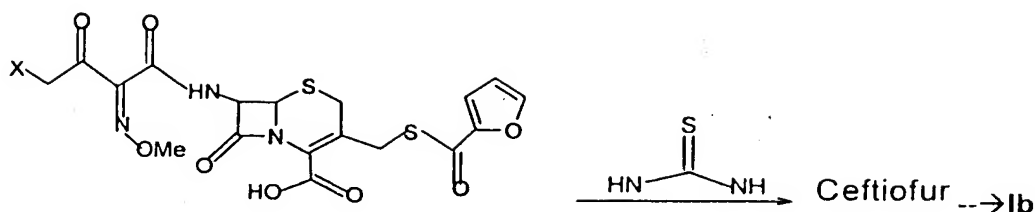
2. US Patent No. **US 4937330** describes a method for preparation of ceftiofur sodium comprising:

- i) neutralizing the mineral acid salt of ceftiofur, specially the hydrochloride salt in an aqueous organic solvent by treating it with a basic resin; eg. Polyvinyl pyridine.
- ii) filtering the solution prepared in step i) to remove the basic resin;
- iii) treating the filtrate obtained in step ii) with a base of an alkali earth metal.

However this method is lengthy and is not cost-effective since it involves the step of formation of a hydrochloride salt and its subsequent neutralization. Moreover, this process utilizes costly resins like poly vinyl pyridine.

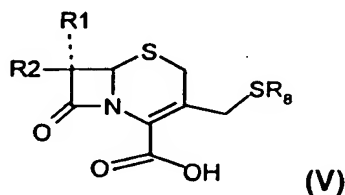
3. US Patent No. **US 6458949** describes a process for preparation of ceftiofur sodium and its intermediates starting from 7-amino—3-(2-furylcarbonylthiomethyl) —3-cephem—4-carboxylic acid (furaca) of formula (III). Furaca is treated with 4-halo-2-methoxyimino-3-oxobutyl halide to give an intermediate, which on cyclization with thiourea gives ceftiofur as shown below:



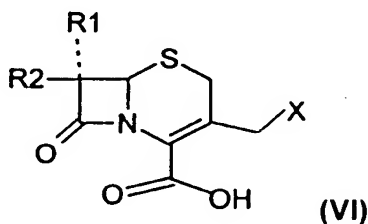


However, this method involves a total of 6 steps, of which 4 steps are involved to prepare the 4-halo-2-methoxyimino-3-oxobutyl halide intermediate, making it lengthy and tedious. Moreover, the yields reported are low rendering the process commercially not very attractive.

4) US Patent No. **US 4312986** discloses a process for producing a 7-(substituted)-amino-3-substituted thiomethyl- Δ^3 -cephem-4-carboxylic acid derivative of the formula (V) comprising



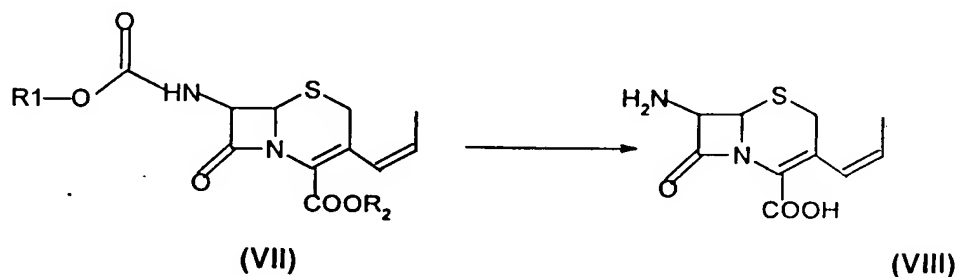
reaction of the compound of general formula (VI)



wherein R₁ is a hydrogen atom or a C₁₋₄ alkoxy group; R₂ inter alia is essentially an amino group, X is a leaving group; with a thiol compound of formula R₈-SH, where R₈ is a thiol compound residue, in an organic solvent in the presence of a protonic acid, or a Lewis acid or complex compound of Lewis acid other than BF₃.

However, this invention essentially teaches the functionalisation at 3-position of compounds of formula (VI), which have a free amino group at 7-position of the cephalosporin nucleus. There is, however, no suggestion that 7-acylamino cephalosporins, specially those carrying a 2-aminothiazoyl acetamido moiety at the 7-position could be reacted with a thiol compound, R_8-SH , in the presence of protonic acids or Lewis acids, to give the corresponding 7-(2-aminothiazoyl)- acetamido-3-substituted thiol derivative.

5) Protonic acids or Lewis acids are known to effect the cleavage of the amide bond at 7-position of a cephalosporins. Incidentally, US Patent No. **US 5132419** relates to a process for preparation of 7-amino-3- [(Z)-1-propen-1-yl]-3-cephem-4-carboxylic acid of formula (VIII), by reaction of the corresponding 7-acyl amino derivative of formula (VII), wherein the cleavage of the amide bond at 7-position is effected by utilization of a protonic acid or Lewis acid.



From this it is abundantly clear that 7-acylamino cephalosporins are highly susceptible to cleavage of the amide bond, in the presence of a protonic acid or a Lewis acid, to give the corresponding 7-amino derivatives.

In view of the above, reaction of compound of formula (VI), wherein, R_2 is an acylamino function specially a 2-aminothiazoyl acetamido moiety with the thiol compound, R_8-SH in the presence of a protonic acid or a Lewis acid could be expected to cleave the amide bond leading to predominant formation of deacylated products.

Surprisingly the present inventors have found that reaction of 7-[2-(2-amino-4-thiazoyl)-2-methoxyimino acetamido] cephalosporanic acid i.e. cefotaxime or

its salts or its easily hydrolysable esters of formula (IX), with a thiol compound R_8-SH , in the presence of a large excess of a protonic acid or a Lewis acid leads to formation of substantial amounts of the 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo- [4.2.0] oct-2-ene-2-carboxylic acid i.e. ceftiofur of formula (Ia) and its sodium salt of formula (Ib) with minimum amounts of the deacylated product i.e. 7-ACA of formula (II), which forms the basis of the present invention.

SUMMARY OF THE INVENTION

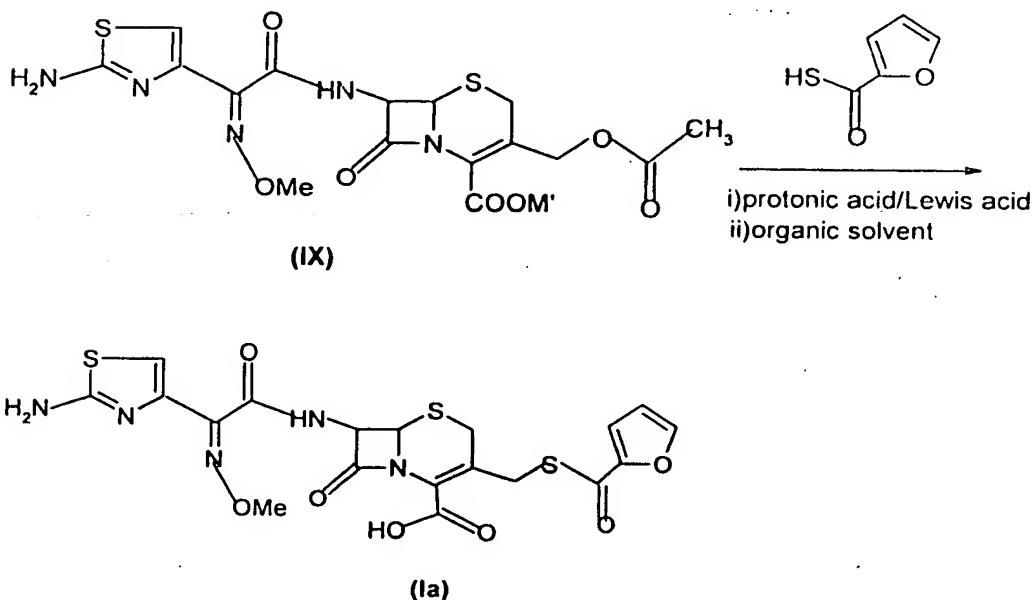
An aspect of the present invention is to provide an improved and cost effective industrial process for the preparation of ceftiofur of formula (Ia) and its sodium salt of formula (Ib) comprising

- i) reaction of cefotaxime or its salts or its esters of formula (IX) with thiofuroic acid in the presence of an organic solvent and in the presence of a protonic acid or a Lewis acid or a mixture thereof to give ceftiofur of formula (Ia),
- ii) converting the ceftiofur of formula (Ia) thus obtained to a salt with an organic amine by treating a solution of ceftiofur in an aqueous organic solvent with an equimolar or slight excess of an equimolar amount of an organic amine, and
- iii) reaction of the amine salt thus obtained with a sodium metal carrier in an aqueous organic solvent in presence of $NaHSO_3$ to give ceftiofur sodium of formula (Ib) and its isolation by conventional methods.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, typically compound of formula (IX) is suspended in an organic solvent, to which the protonic acid or the Lewis acid is added. To the resulting solution is added thiofuroic acid and the progress of

the reaction is monitored by HPLC. After completion of reaction the product i.e. ceftiofur of formula (Ia) is isolated by conventional methods.

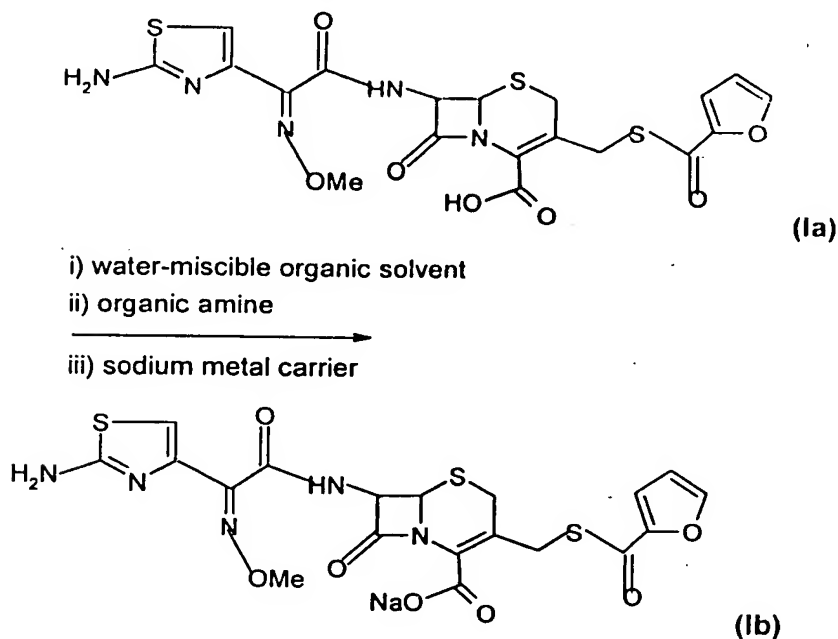


wherein M' is H, an alkali or alkaline earth metal, or easily hydrolysable ester.

By easily hydrolysable esters of the compounds of formula (IX) there are to be understood compounds of the formula (IX) in which the carboxyl group is present in the form of an ester group which can be easily hydrolysed. Examples of such esters, which can be of the conventional type, are the lower alkanoyloxyalkyl esters, e.g., the acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, 1-pivaloxyethyl ester; the lower alkoxycarbonyloxyalkyl esters, e.g., the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester, the alkoxymethyl esters, e.g., methoxy methyl ester, and the lower alkylaminomethyl esters, e.g., the acetamidomethyl esters. Other esters, e.g. the benzyl and cyanomethyl esters can also be used.

The ceftiofur acid thus obtained is suspended in a mixture of water-miscible organic solvent and water, to which the organic amine is added to obtain a solution of the salt of ceftiofur with the organic amine. The amine salt thus

obtained can be isolated, but preferably without isolation is reacted with a sodium metal carrier to give ceftiofur sodium of formula (Ib).



As the protonic acids, there may be exemplified pyrophosphoric acid, pyrosulfuric acid, sulfuric acids, sulfonic acids and super acids. The term "super acid" used herein means acids stronger than 100% sulfuric acid and includes a part of the sulfonic acids and sulfuric acids. More specifically, the sulfuric acids include sulfuric acid, chloro sulfuric acid, fluoro sulfuric acid and the like, and the sulfonic acids include alkyl- (mono or di-) sulfonic acids such as methanesulfonic acid, trifluoromethane sulfonic acid and the like and aryl (mono-, di- or tri-) sulfonic acids such as benzene sulfonic acid, naphthalene sulfonic acid, p-toluene sulfonic acid and the like. The super acid includes perchloric acid, magic acid ($\text{FSO}_3\text{H-SbF}_5$), $\text{FSO}_3\text{H-AsF}_5$, $\text{CF}_3\text{SO}_3\text{-H-SbF}_5$, $\text{H}_2\text{SO}_4\text{-SO}_3$ and the like.

The Lewis acid include, for example, aluminium chloride, boron trifluoride, zinc halides and tin halides, and more specifically include zinc chloride, zinc bromide, stannic chloride, stannic bromide and the like. The complex compounds of Lewis acid include complex salts of the above-mentioned

Lewis acid with dialkyl ethers, amines, fatty acids, nitriles, carboxylic esters and phenols. The above mentioned sulfonic acids may be substituted by halogen atoms such as chlorine, bromine and the like, carboxyl groups, sulfo groups, nitro groups, lower alkyl groups, and lower alkoxy groups.

Organic amines that can be used in the invention are selected from the group of triethyl amine, diethyl amine, cyclohexyl amine, tertiary butyl amine, benzyl amine and the like.

Sodium metal carriers can be either organic or inorganic selected from both organic and inorganic and the examples include sodium hydroxide, sodium carbonate, sodium bi carbonate, sodium ethoxide, sodium-2-ethyl hexanoate, sodium acetate, sodium propionate, sodium salt of 2-ethylcaproic acid and the like.

Example 1:

Preparation of 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur) from 7-[2-(2-amino-4-thiazolyl)-2-methoxyimino acetamido] cephalosporanic acid (cefotaxime) (IX):

20.0g (0.044 moles) of 7-[2-(2-amino-4-thiazolyl)-2-methoxyimino acetamido] cephalosporanic acid (cefotaxime) and acetonitrile (200 ml) was charged to a round bottom flask. Reaction mixture was cooled to 0-5 °C. Methane sulfonic acid 62.0g (0.643 moles) followed by thiofuroic acid 50.0ml (0.066 moles) was added. Temperature of the reaction mixture was raised to 10-15 °C. Progress of reaction was monitored by HPLC. After completion of reaction the reaction mixture was cooled to 0 °C. Reaction mixture was filtered and washed with 2x100 ml of ethyl acetate. The solid cefotaxime (IX) obtained was taken in 200 ml of de-mineralized water, cooled to 10 °C and the pH was adjusted to 3.0 by addition of 10% HCl and the said precipitate was filtered off.

The wet solid thus obtained was taken in 200 ml of demineralised water and cooled to 10 °C. 100 ml of ethyl acetate and 40 ml of acetonitrile was added. The pH was adjusted to 7.0 by addition of aqueous sodium carbonate solution (17%). The pH of the solution was readjusted to 3.0 by dilute HCl (15%). The

organic and aqueous layer was separated and the organic layer was added 100 ml of cyclohexane at 27 °C. The solid was filtered and washed with cyclohexane (100 ml) to give 5.0g (25%) of 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur).

Example 2:

Preparation of 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur) from cefotaxime sodium (IX):

20g of cefotaxime sodium (0.04192 moles) and acetonitrile (200ml) were charged in a round bottom flask at room temperature. Mixture was cooled and methanesulfonic acid (62g, 0.642 mole) was added slowly to the reaction mixture. Thiofuroic acid 50 ml. (0.066 moles) was added to the reaction mixture in a single lot. Reaction mixture was stirred for three hours. Progress of reaction was monitored by HPLC. The reaction mixture was cooled to 0°C and the solid filtered and washed with 2X100ml ethyl acetate. The wet cefiofur (Ia) was taken in 200 ml of demineralised water, cooled to 10 °C and pH of the solution was adjusted to 3.0 by 10% HCl. The solution was filtered and washed with demineralised water.

The wet solid cefiofur was taken in 100 ml of ethyl acetate and 40 ml of acetonitrile and pH of the solution is adjusted to 7.0 by 17% aqueous solution of sodium carbonate. The pH was readjusted to 3.0 by dilute HCl (15%). The organic and aqueous layers were separated and to the organic layer was added 400 ml of cyclohexane at 27 °C. The solid was filtered and washed with 100 ml of cyclohexane to yield 5.0g (25%) of 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur) having purity of 96.11%.

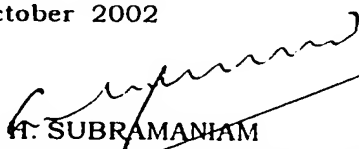
Example3:

Preparation of cefiofur sodium (Ib) from 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur) (Ia):

140 ml of THF and 4.0 ml of demineralised water (DMW) and 4.0g (0.00764 moles) of 7-[2-(2-amino-4-thiazolyl) glyoxylamido] 3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (ceftiofur) was taken in a flask and stirred. Reaction mixture was cooled and 0.81g (0.0080 moles) of triethyl amine (TEA) was added. Activated carbon (0.60g) and sodium dithionite (0.04g) was added and the reaction mixture was stirred. The mixture was filtered through celite bed and washed with a mixture of THF and DMW. The filtrate was passed through 0.2 μ filter paper and washed with THF (100 ml).

A solution of sodium-2-ethyl hexanoate (1.80g, 0.01084 moles) was prepared in THF and passed through 0.2 μ filter paper. This filtrate was added gradually in the reaction mixture. The mixture was filtered under nitrogen atmosphere. The wet cake was slurry washed by THF followed by ethyl acetate (2X44 ml) and acetone (2X29 ml). The wet cake was dried under nitrogen atmosphere for 30-45 minutes with occasional stirring. The semi dry cake was dried in vacuum oven at 700mmHg/40°C till moisture content is 2.0% and other volatile impurities are under prescribed limits. The yield of 98.0% pure Ib was reported to be 3.48g (87%).

Dated this the 26th day of October 2002


H. SUBRAMANIAM
Subramaniam, Nataraj & Associates
Attorneys for the applicants